UNIVERSITY OF PENNSYLVANIA

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# I. ALPHA-BROMO-ALPHA-SULFONYLAMIDES
# II. ALPHA-BROMOSULFONES

A DISSERTATION

IN CHEMISTRY

PRESENTED TO THE FACULTY OF THE GRADUATE SCHOOL IN
PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY

WILLIAM M. ZIEGLER

PHILADELPHIA

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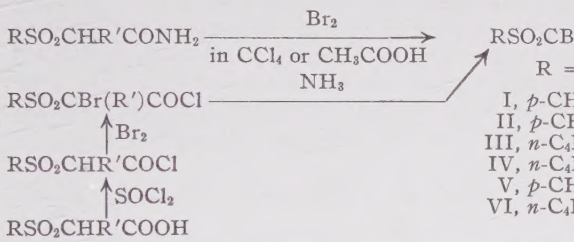
# α-Bromo-α-sulfonylamides[1]

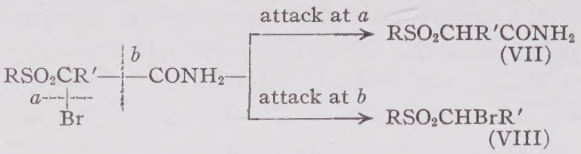
By William M. Ziegler[2]

This study of α-bromo-α-sulfonylamides was undertaken for the purpose of comparing their reactions with those of the bromo derivatives of other active methylene compounds. While some reactions of the latter resemble the reactions of hypohalites ("positive halogen"[3]) rather than of halides, the ability of the sulfone group to produce this type of activation has heretofore received little attention.[4] No α-bromo-α-sulfonylamides appeared to have been prepared previously and it was first necessary to devise methods for their synthesis. Since the α-bromo-α-sulfonylamides were found to have properties identical with those of the compounds previously reported to be the isomeric N-bromoamides, the establishment of their structure constitutes a third phase of this report.

**Preparation of α-Bromo-α-sulfonylamides.**—Two of the α-bromo-α-sulfonylamides (I and IV) were prepared by converting α-sulfonyl acids to acid chlorides, bromination and treatment with ammonia. The method was laborious and the yields low. Much better results were obtained by treating α-sulfonylamides with bromine in moist[6] carbon tetrachloride and all of the α-sulfonylamides tested reacted readily under these conditions. Glacial acetic acid was satisfactory as a solvent for the preparation of I and III but the α-sulfonyl-*n*-butyramides were not brominated in this solvent.




**Reactions of α-Bromo-α-sulfonylamides.**—The reactions of these compounds were of two types. One resulted in the oxidation of the reagent and reduction of the α-bromoamide, showing the positive character of the halogen. The other type resulted in the cleavage of the —$CONH_2$ group. The predominant reaction depended both upon the reagent and upon the structure of the α-bromo-α-sulfonylamide. For example, sodium ethoxide gave the reduction product (VII) from IV but caused elimination of the —$CONH_2$ group from I to give the α-bromosulfone (VIII). Furthermore, II was not hydrolyzed under conditions which converted I to the α-bromosulfone[7] (VIII) and which resulted in attack at both the —Br and —$CONH_2$ groups of IV.




Two of the results reported in Table I are of especial importance. The liberation of two equivalents of iodine by the dibromo amides with potassium iodide in acid solution is contradictory to the report of Tröger and Hille that only one halogen atom of the dibromo amides underwent this reaction. It is also interesting to note that the time for complete reaction of the dibromo compounds with hydrazine was less than that for the corresponding monobromo compounds. It may therefore be inferred that this reaction is not stepwise and that the monobromo derivatives

(1) This communication is a portion of a thesis submitted by William M. Ziegler in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the University of Pennsylvania in June, 1939.

(2) Harrison Fellow in Chemistry, 1938–1939.

(3) Waters, "Physical Aspects of Organic Chemistry," 2nd ed., George Routledge and Sons, London, 1937, p. 221.

(4) The results of Tröger and Hille[5] indicated that α-bromo-α-sulfonylamides do not contain positive halogen. Since our problem was begun, Samen [*Arkiv Kemi, Mineral. Geol.*, **12B**, No. 51 (1938); *Chem. Abs.*, **32**, 4520 (1938)] reported that triethylsulfonylmethyl bromide was reduced to triethylsulfonylmethane by treatment with hydrazine or hydriodic acid, and Mellander [*ibid.*, **12A**, No. 16, 32 (1937); *Chem. Abs.*, **31**, 5763 (1937)] found that α-bromo-α-sulfonyl acids were reduced by hydrazine.

(5) Tröger and Hille, *J. prakt. Chem.*, [2] **71**, 201 (1905).

(6) Water alone could not be used as a reaction medium, probably because of the insolubility of the α-sulfonylamides. Bromination occurred more slowly or not at all in dry carbon tetrachloride, suggesting that the reaction is similar to the basic catalysis in the bromination of ethyl acetoacetate [Pederson, *J. Phys. Chem.*, **38**, 601 (1934)]. However, aqueous sodium hypobromite was a less favorable reagent for halogenation of α-sulfonylamides than was bromine in moist carbon tetrachloride.

(7) The result of this hydrolysis was unexpected. According to Mossler [*Monatsh.*, **29**, 73 (1908)] α-bromoamides give aldehydes upon alkaline hydrolysis. A N-bromoamide would be expected to give an amine.[8]

are not intermediates in the reduction of the dibromo amides with hydrazine.

The reactions of the α-bromo-α-sulfonylamides with hydrazine, hydriodic acid, piperidine and mercaptides gave VII accompanied by nitrogen, iodine, piperidine hydrobromide and disulfide, respectively. Since similar results have been obtained with the bromo derivatives of active methylene compounds, it may be concluded that the sulfone group exerts upon halogen in the *alpha* position an effect similar to that of other labilizing groups.

**Structure of the Bromoamides.**—There seemed no reasonable doubt that the syntheses involving bromination of the acid chlorides would give α-bromo-α-sulfonylamides. However, I, prepared by this method, was identical with the product obtained by bromination of the α-sulfonylamide in glacial acetic acid by the procedure of Tröger and Hille[5] and reported by those workers to be a N-bromoamide (IX). Furthermore, IV prepared from the α-bromoacid chloride was identical with the products obtained by the method of Tröger and Hille and by bromination of the α-sulfonylamide in moist carbon tetrachloride. There seems to be little doubt, therefore, that the compounds assigned structures IX and X by Tröger and Hille are actually I and V.

$$p\text{-}CH_3C_6H_4SO_2CH_2CONHBr$$
IX

$$p\text{-}CH_3C_6H_4SO_2CHBrCONHBr$$
X

Attempts further to confirm the structures by synthesis of the isomeric N-bromoamides by bromination in the presence of alkali were unsuccessful because of the failure of the amides to react or the formation of dibromosulfones. The α-bromo-α-sulfonylamides did not react with nitrous acid and their conversion to α-bromo acids was therefore unsuccessful.

It should be pointed out that the arguments of Tröger and Hille for a N-bromo structure for these compounds were based largely upon the statement that the dibromoamides reacted with only one equivalent of iodide, a statement now shown to be incorrect. If further evidence for the attachment of bromine to carbon is necessary it may be gained from the following. (a) The compounds are stable toward boiling water.[8] (b) The difference in the ease of bromination of the acetamides and butyramides would not be expected to be so great if it depended upon the influence of an *alpha* ethyl group upon the reactivity of —$CONH_2$. (c) The conversion of I to an α-bromosulfone (VIII) by hydrolysis further establishes the position of the halogen.[9]

(8) Hofmann [*Ber.*, **15**, 411 (1882)] reported that N-bromoamides are decomposed by boiling water.

## Experimental Part[10]

**Reactions of α-Sulfonylamides[11] with Sodium Hypobromite.**—To 21.4 g. of α-*p*-tolylsulfonylacetamide[12] was added 5.4 ml. (16 g.) of bromine, and the mixture shaken until about three-fourths of the amide had dissolved. The mixture was cooled in an ice-bath at −15° and a cold solution of 50% sodium hydroxide added dropwise with stirring until 10% more than the theoretical amount required to react with the bromine had been used. After standing in the ice-bath for one hour, cold water was added, the product removed by filtration and recrystallized from alcohol. The yield of *p*-tolylsulfonyldibromomethane, m. p. 116–117°,[9] was 2.9 g. (18% based on the bromine).

In another experiment 10.3 g. of α-*n*-butylsulfonyl-*n*-butyramide was mixed with 5.4 ml. (16 g.) of bromine and treated as described above. Unchanged starting material was the only product isolated.

### Preparation of α-Bromoamides from Acid Chlorides

**α-Bromo-α-*p*-tolylsulfonylacetamide (I).**—To 21.4 g. of *p*-tolylsulfonylacetic acid[13] in 75 ml. of carbon tetrachloride, 13 g. of thionyl chloride in 25 ml. of carbon tetrachloride was added slowly. After refluxing for one hour and cooling, 6 ml. (18 g.) of bromine was added and the mixture then refluxed for ten hours, cooled, and poured into excess concentrated ammonia water at −15°. The lump that formed on stirring was removed and extracted several times with the same 200 ml. of water, cooling and removing the crystals between extractions. The crystals thus removed were recrystallized from water with the aid of charcoal. The yield was 2.40 g. (8%), m. p. 172–174°.

*Anal.* Calcd. for $C_9H_{10}O_3NSBr$: Br, 27.3. Found: Br, 27.2, 27.5.

**α-Bromo-α-*n*-butylsulfonyl-*n*-butyramide (IV).**—From 136.5 g. of ethyl α-bromo-*n*-butyrate and the mercaptide from 54.6 g. of *n*-butyl mercaptan under the conditions previously used for the preparation of the amides,[11] there was obtained 105 g. (74%) of crude ethyl α-*n*-butylthio-*n*-butyrate which was oxidized[11] in acetic acid–acetic anhydride mixture to the α-sulfonyl ester. The ester could not be crystallized and decomposed upon attempted dis-

(9) The formation of VIII might be considered possible from a N-bromoamide by hydrolysis of the latter to sodium hypobromite, followed by the action of the hypobromite upon the other hydrolysis products. This explanation of the hydrolysis result was eliminated by showing that none of the hydroylsis products were converted to VIII by sodium hypobromite.

(10) All melting points are corrected unless otherwise specified.

(11) The α-sulfonylamides were prepared by the methods described by d'Ouville and Connor, *J. Am. Chem. Soc.*, **60**, 33 (1938), and Pomerantz and Connor, *ibid.*, **61**, 3386 (1939).

(12) Similar results were obtained when sodium *p*-tolylsulfonylacetate was used but methyl *p*-tolyl sulfone did not react under these conditions.

(13) Gabriel, *Ber.*, **14**, 833 (1881).

tillation. The crude material was hydrolyzed with 400 ml. of 8% sodium hydroxide solution, acidified and extracted with ether. The acid obtained (93.6 g.) was converted to the acid chloride under the conditions described above, refluxed with bromine (71 g.) for twenty-five hours and treated with an excess of dry ammonia. The solvent was decanted, the residue extracted with alcohol and the alcohol solution treated with decolorizing charcoal. Removal of the solvent gave an oil which was crystallized with considerable difficulty. The solid was recrystallized several times from ether, seeding each time. The yield was 10.75 g. (6% based on the mercaptan), m. p. 56–57°. This was slightly less pure than the material obtained as described below.

*Anal.* Calcd. for $C_8H_{16}O_3NSBr$: Br, 27.9. Found: Br, 27.1, 27.2.

**Preparation of α-Bromo-α-sulfonylamides from α-Sulfonylamides.**—Five hundredths mole of the amide[11] was mixed with 100 ml. of carbon tetrachloride and 2.66 ml. (8 g.) of bromine added. With the acetamides the moisture present in unpurified carbon tetrachloride was adequate but the bromination of the butyramide was accomplished more readily by the addition of 2 ml. of water. After refluxing until the bromine color had disappeared, the solvent was removed quickly and the oil recrystallized. Slow removal of the solvent resulted in hydrolysis. A prolonged reaction period in the presence of excess water gave the dibromosulfonylmethane as shown below under the preparation of I.

**α-Bromo-α-*p*-tolylsulfonylacetamide** (I).—The mixture, without additional water, was refluxed for one hour and the solvent removed over a period of twenty minutes. The oil was dissolved in alcohol and allowed to crystallize. The solid was recrystallized from alcohol. From 10.7 g. of the amide there was obtained 6 g. (42%) of the product, m. p. 172–174°. The same product (51%) was obtained by the method of Tröger and Hille.[5] Neither sample lowered the melting point of the amide prepared from the α-bromo-α-sulfonyl acid chloride.

*Anal.* Calcd. for $C_9H_{10}O_3NSBr$: Br, 27.3; N, 4.80. Found: Br, 27.4, 27.6; N, 4.85, 4.80.

Ten and seven-tenths grams of α-*p*-tolylsulfonylacetamide in 100 ml. of carbon tetrachloride and 4 ml. of water was treated with 2.66 ml. (8 g.) of bromine and refluxed for one-half hour. The solution was then poured into a beaker and evaporated on a water-bath over a period of four hours. The sirup was dissolved in ether and filtered, the ether was then evaporated and the oil well chilled. After several hours chilling the paste that formed was mixed with enough very cold ether to dissolve the oily impurities and the material was filtered. The crystals were recrystallized from ligroin (b. p. 70–90°) and then from alcohol. The yield was 2.3 g. (28% based on the bromine) of product melting 116–117°, reported by Tröger and Hille[5] to be the melting point of *p*-tolylsulfonyldibromomethane.

**α-Bromo-α-*p*-tolylsulfonyl-*n*-butyramide** (II).—Two milliliters of water was added and the mixture refluxed for two and one-half hours. Half the solvent was removed and the material chilled. The product was recrystallized four times as follows: it was dissolved in a hot mixture of 75% carbon tetrachloride–25% ether, cooled and filtered. Then it was dissolved *immediately* in ether; failure to do so resulted in a product insoluble in ether. Just as solution was complete the product precipitated. It was removed by filtration and the process repeated. Twelve grams of amide gave 6.8 g. (43%) of product, m. p. 115–116°.

*Anal.* Calcd. for $C_{11}H_{14}O_3NSBr$: Br, 25.0; N, 4.38. Found: Br, 25.3, 25.0; N, 4.45, 4.44.

**α-Bromo-α-*n*-butylsulfonylacetamide** (III).—The mixture, without additional water, was heated for three-fourths hour and the solvent removed in twenty minutes. The oil was dissolved in alcohol, cooled and the product recrystallized once from benzene and twice from water. Nine grams of amide gave 5.75 g. (44%) of product, m. p. 130–131°. The procedure of Tröger and Hille[5] gave a 31% yield of the same material.

*Anal.* Calcd. for $C_6H_{12}O_3NSBr$: Br, 31.1; N, 5.45. Found: Br, 31.1, 31.0; N, 5.46, 5.50.

**α-Bromo-α-*n*-butylsulfonyl-*n*-butyramide** (IV).—The mixture with 2 ml. of water was refluxed for two hours and the solvent removed in twenty minutes. The oil was cooled and a seed crystal added. Seeding was also necessary in recrystallizing the product from ether. To obtain a seed crystal, a little of the oil was dissolved in ether and ligroin added to turbidity, then cleared with ether. The solution was allowed to stand open for three days, when the oil which first precipitated was crystallized. From 10.3 g. of the amide, 8.3 g. (58%) of product, m. p. 57–58°, was obtained. A mixed melting point with the product from the acid chloride was 56–58°.

*Anal.* Calcd. for $C_8H_{16}O_3NSBr$: Br, 27.9; N, 4.89. Found: Br, 27.7, 27.8; N, 4.74, 4.75.

**α,α-Dibromo-α-*p*-tolylsulfonylacetamide** (V).—The mixture without water but with 5.3 ml. of bromine was heated for two and one-half hours and the solvent removed in twenty minutes. The oil was taken up in alcohol and crystallized by cooling. It was then recrystallized from alcohol. The product from 10.7 g. of amide was 2.1 g. (11%), m. p. 134–135°.

*Anal.* Calcd. for $C_9H_9O_3NSBr_2$: Br, 43.1; N, 3.77. Found: Br, 43.3, 43.3; N, 3.65, 3.68.

**α,α-Dibromo-α-*n*-butylsulfonylacetamide** (VI).—This was obtained as a by-product in the preparation of III by the method of Tröger and Hille as mentioned above. The reaction mixture from 9 g. of α-*n*-butylsulfonylacetamide in 35 ml. of glacial acetic acid with 8 g. of bromine for one hour at room temperature was poured onto cracked ice and the III removed by filtration. The filtrate, after standing for three hours, gave a precipitate of VI which was recrystallized from dilute alcohol. The yield of VI was 1.8 g. (19%), m. p. 106–107°.

*Anal.* Calcd. for $C_6H_{11}O_3NSBr_2$: Br, 47.6; N, 4.17. Found: Br, 47.4, 47.6; N, 4.25.

### Reactions of α-Bromo-α-sulfonylamides

**With Sodium *n*-Butyl Mercaptide.**—Four-tenths gram of sodium was dissolved in 30 ml. of absolute alcohol, and 1.7 ml. of *n*-butyl mercaptan added. This was cooled in a salt–ice-bath and a suspension prepared by dissolving 5.4 g. of II in 10 ml. of absolute alcohol and chilling, was added. The mixture was allowed to come to room temperature as the bath melted and then stand for five days.

The alcohol was evaporated to a small volume and the product poured onto chipped ice. The crystalline material was removed by filtration and recrystallized from water. The product was 2.45 g. (60%) of α-*p*-tolylsulfonyl-*n*-butyramide, m. p. 170–171°.

**With Sodium *n*-Thiocresolate.**—To 0.23 g. of sodium in 25 ml. of absolute alcohol was added 1.25 g. of *p*-thiocresol, then 2.85 g. (0.01 mole) of IV. The mixture was allowed to stand for five days and was then evaporated under reduced pressure until crystals separated. The residue was poured onto cracked ice, the product removed by filtration and recrystallized from alcohol. The product, 1 g. (80%), m. p. 45–46°, was ditolyldisulfide. Evaporation of the alcoholic and aqueous mother liquors gave, on recrystallization from water, 1.5 g. (73%) of α-*n*-butylsulfonyl-*n*-butyramide.[14]

This experiment was repeated using dioxane as a solvent and preparing the thiocresolate by the reaction of powdered sodium with *p*-thiocresol. There were isolated 0.75 g. (60%) of ditolyldisulfide, 0.72 g. (35%) of α-*n*-butylsulfonyl-*n*-butyramide and an oil from which nothing could be separated.

**With Hydriodic Acid and with Hydrazine.**—See Table I.

**With Piperidine.**—Six milliliters of piperidine dissolved in 10 ml. of dry dioxane was added to 6.25 g. of I dissolved in 40 ml. of dry dioxane and the mixture refluxed for seven hours. The crystalline precipitate was removed by filtration and washed with a little dioxane. The filtrate was evaporated to a smaller volume, removing both dioxane and piperidine, cooled and again filtered. The residue was washed with a little dioxane and added to the first one. The yield was 2.15 g. (60%) of piperidine hydrobromide,[15] m. p. 233–235°. Further evaporation of the filtrate resulted, on cooling and filtering, in a 2 g. (45%) yield of α-*p*-tolylsulfonylacetamide, m. p. 166–167°. Evaporation of this filtrate resulted in an oil from which nothing separated.

**With Sodium Ethoxide.**—To 50 ml. of absolute alcohol was added 0.23 g. of sodium. After the reaction was completed, the solution was cooled and 2.92 g. (0.01 mole) of I was added. The mixture was allowed to stand for two days at room temperature. Most of the alcohol was removed by distillation and a volume of water equal to the residue was added. On cooling and filtering 2.10 g. (84%) of *p*-tolylsulfonylmethyl bromide, m. p. 87–88°, was obtained. The identity of this compound was established by a mixed melting point with a sample prepared by a method to be described in a later paper.

To 25 ml. of absolute alcohol was added 0.23 g. of sodium. After the reaction was completed, the solution was cooled and 2.86 g. of IV was added. This was allowed to stand for four days, then most of the alcohol was evaporated, the residue poured into water and the mixture chilled. The resulting paste was recrystallized from alcohol and then water and gave 1.25 g. (61%) of α-*n*-butylsulfonyl-*n*-butyramide, m. p. 120–122°. The filtrates on evaporation gave a small quantity of oil.

(14) These reactions are comparable to the formation of di-*p*-tolyldisulfide and tribenzoylmethane from the sodium salt of *p*-thiocresol and tribenzoylmethyl chloride as reported by Kohler and Potter, *J. Am. Chem. Soc.*, **58**, 2168 (1936).

(15) Similar dehalogenations have been observed frequently; for example, Cope, *ibid.*, **54**, 1250 (1932).

TABLE I

REACTIONS OF α-BROMO-α-SULFONYLAMIDES

| Amide | With HI,[a] % Br | | With $H_2NNH_2$[b] $N_2$ (ml.) | | Reaction time (hr.) | IX isolated % |
|---|---|---|---|---|---|---|
| | Calcd. | Found | Calcd. | Found | | |
| I | 27.4 | 28.2 | 44.8 | 45.0 | 5 | 82 |
| II | 25.0 | 24.3 | 39.5 | 39.0 | 4 | 87 |
| III | 31.1 | 32.2 | 47.5 | 46.5 | 2 | 80 |
| IV | 27.9 | 27.6 | 40.8 | 31.0 | 6 | 82 |
| V | 43.1 | 38.6 | 29.5[c] | 30.0 | 1 | 83 |
| VI | 47.6 | 47.0 | 32.6[d] | 33.0 | 1 | 47[d] |

[a] Ten drops of 16 *N* sulfuric acid and 2 ml. of saturated potassium iodide solution were added to a solution of about 0.1 g. of the α-bromoamide in 15 ml. of glacial acetic acid. The flasks were stoppered and allowed to stand for thirty minutes with occasional shaking. The mixture was then titrated with 0.1 *N* sodium thiosulfate solution, using the disappearance of iodine color as an end-point and confirming by the addition of 0.5 ml. of 1% starch solution. Blanks were run in all experiments and, since they amounted to 10–15% of the total readings, the results reported are not considered to be quantitative. The data do show, however, that at least 90–95% of the total bromine in the compounds is able to oxidize hydriodic acid and that the observations of Tröger and Hille on the dibromo-*p*-tolylsulfonylacetamide were in error. [b] Except as otherwise indicated, about 1.00 g. of the α-sulfonyl-α-bromoamide was added to 15 ml. of water in a 50-cc. flask and a small tube containing 3.0 ml. of 10% hydrazine hydrate solution placed upright in the flask. This was then put in a water-bath at 75 ± 2°, allowed to come to this temperature, connected to a gas measuring apparatus, and the contents mixed. The mixture was kept at 75° and shaken occasionally until the evolution of nitrogen ceased. The contents of the flask were concentrated, chilled and the α-sulfonylamide removed by filtration, dried and weighed. [c] The sample weighed 0.45 g. [d] The sample weighed 0.50 g. The low recovery may be attributed to the difficulty of isolation of a rather small amount of a fairly soluble product.

**With Nitrous Acid.**[16]—To 5.4 g. of I dissolved in 50 ml. of alcohol–acetic acid (1:4) and kept cool, 2.6 cc. of *n*-butyl nitrite was added. The mixture was allowed to stand for twenty-four hours. Then hydrochloric acid was added and the mixture again allowed to stand for twenty-four hours; 80% of the bromoamide was recovered.

Addition of a solution of sodium nitrite to a solution of the bromoamide in acetic acid in the cold gave a 70% recovery. When the mixture was heated to 60° after one hour of standing the recovery was 85%.

**Hydrolysis.**—Two grams of I was sprinkled into 80 ml. of boiling 5% sodium hydroxide solution and the mixture boiled for two and one-half minutes. The material was chilled and filtered. The product was recrystallized from alcohol and yielded 0.78 g. (45%) of material melting at 89–90°. A mixed melting point with a sample of *p*-tolylsulfonylbromomethane (m. p. 90–91°) was 89–91°. This hydrolysis was carried out on the bromoamide pre-

(16) These experiments were carried out in an attempt to convert the amides to α-bromoacids as additional confirmation of their structure.

pared from the bromoacid chloride as well as that from the bromination of the amide in carbon tetrachloride. No trace of the α-sulfonyl acid was observed when the filtrate from the reaction mixture was acidified. Addition of silver nitrate solution gave silver bromide, indicating some hydrolysis of the halide.

Into 50 ml. of boiling 5% sodium hydroxide solution was sprinkled 2.86 g. of IV. The mixture was boiled about five minutes until only a faint test for ammonia was obtained. It was then chilled, acidified with nitric acid and extracted with ether. The aqueous portion gave a heavy precipitate with silver nitrate, indicating a large removal of bromine. The ether extracts were evaporated and gave a small quantity of oil that did not solidify at −15°. The amount of oil was less than 1 ml.

Two grams of II was sprinkled into 50 ml. of boiling 5% sodium hydroxide solution. The material formed opaque globules and only traces of ammonia were evolved. The mixture was refluxed for five minutes, chilled and filtered. The entire residue was unchanged amide.

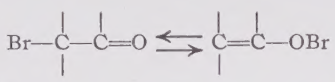
## Summary

Compounds reported to be N-bromo-α-sulfonylamides by Tröger and Hille have been shown to be α-bromo-α-sulfonylamides. The most satisfactory method of preparation of α-bromo-α-sulfonylamides was by direct bromination of α-sulfonylamides in moist carbon tetrachloride. Members of this series were also prepared by direct bromination of the amides in glacial acetic acid and by bromination of α-sulfonyl acid chlorides, followed by reaction with ammonia. The reactions of α-bromo-α-sulfonylamides showed that the sulfone group was similar to other labilizing groups in causing hypohalite characteristics in α-halo derivatives.

# α-Bromosulfones[1]

By William M. Ziegler[2]

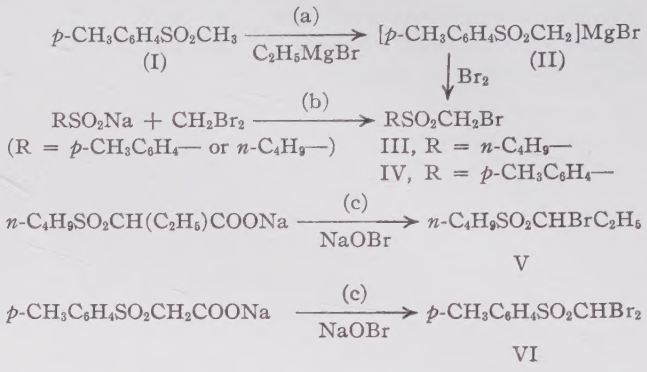
The influence of labilizing groups (such as —COOR, —COR, —CN, etc.) upon an adjacent substituent may be attributed partly to the electron-attracting properties of these groups and partly to the ability of the groups to participate in reactions. Thus in α-bromo ketones the reactivity of the halogen does not depend entirely upon the polar influence of the keto group upon the carbon–bromine bond, but also upon reactions which involve the carbonyl function. For example, certain reactions[3] of α-bromo ketones occur by preliminary addition to the carbonyl. It has also been suggested[4] that the reaction of "positive halogen"[5] compounds are due to an anionotropic shift



although there is evidence that this is not always true.[6] From these considerations it may be concluded that our usual views of the influence of labilizing groups upon halogen in the alpha position are based upon a summation of many factors involved in the reactions studied.

It seemed that some of these factors would be eliminated, or at least minimized, in the reactions of α-bromosulfones. It has already been pointed out[6] that anionotropy would be unlikely in α-bromosulfones and that addition to the sulfone group would require expansion of the valence shell of sulfur. It might therefore be expected that in α-bromosulfones the labilizing group would have little or no tendency to participate in reactions and that the reactions would give an indication of the importance of the polar character of labilizing groups[7] in influencing the reactivity of alpha halogen.

While our chief interest was in the reactions of α-bromo derivatives of monosulfones, few of these compounds had been described previously[8,9] and it was first necessary to investigate methods for their synthesis. The three methods used were (a) reaction of a sulfone (I) with ethylmagnesium bromide and treatment of the bromomagnesium derivative (II)



with bromine, (b) reaction of the salt of a sulfinic acid with methylene bromide[10] and (c) treatment of an α-sulfonyl acid with bromine in alkaline solution.[11] Method (a), which had not been previously reported, was the most convenient but

(1) This communication is a portion of a thesis submitted by William M. Ziegler in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the University of Pennsylvania in June, 1939.

(2) Harrison Fellow in Chemistry, 1938–1939.

(3) Kohler and Brown, *J. Am. Chem. Soc.*, **55**, 4299 (1933).

(4) Willstätter and Hattenroth, *Ber.*, **37**, 1778 (1904); Howk and McElvain, *J. Am. Chem. Soc.*, **54**, 282 (1932).

(5) Waters, "Physical Aspects of Organic Chemistry," 2d ed., George Routledge and Sons, London, 1937, p. 221.

(6) Kohler and Tishler, *J. Am. Chem. Soc.*, **57**, 218 (1935).

(7) The reactions of α-bromo-α-sulfonylamides [Ziegler and Connor, *ibid.*, **62**, 1049 (1940)] were like the reactions of the α-bromo derivatives of other active methylene compounds. This did not satisfy the purpose of the present investigation, for the C=O of the amide group could participate in the reactions. The results are, however, pertinent to this work because they show that the polar effect of the sulfone group upon halogen is similar to that of other labilizing groups. This seems to be justification for considering that the results obtained with α-bromosulfones are indicative of the polar influences of other labilizing groups.

(8) A few α-halosulfones were reported by Otto [*J. prakt. Chem.*, [2] **40**, 526 (1880)]. Shortly after the completion of this investigation, Shriner and Greenlee [*J. Org. Chem.*, **4**, 242 (1939)] described the bromo derivatives of three nitrobenzyl *p*-tolyl sulfones. Since these compounds contain, in addition to the sulfone group, a second labilizing group (phenyl) and the added influence of vinylogous [Fuson, *Chem. Rev.*, **16**, 1 (1935)] nitro groups, they are more comparable to the compounds described in our previous paper[7] than to the simple α-bromosulfones described here.

(9) The observation of Michael and Palmer [*Am. Chem. J.*, **6**, 253 (1884)] that phenylsulfonylmethyl iodide was dehalogenated by sodium ethoxide indicated that α-halosulfones possessed the reactions of positive halogen. Further indications of this were observed with the bromo derivatives of a disulfone and a trisulfone. Kohler and Tishler[6] reported the dehalogenation of diphenylsulfonyldibromomethane by the Grignard reagent and Samen [*Arkiv. Kemi, Mineral. Geol.*, **12B**, No. 51 (1938)] reported that triethylsulfonylmethyl bromide was reduced to triethylsulfonylmethane by hydrazine or hydriodic acid.

(10) Michael and Palmer[9] used a sealed tube for the reaction of sodium benzenesulfinate with methylene iodide. The reactions reported here occurred in boiling alcohol.

(11) This reaction was reported by Otto.[8]

would not be suitable for use with unsymmetrical dialkyl sulfones because of the probable formation of isomers. Method (b) gave satisfactory results with sodium *n*-butanesulfinate but aromatic sulfinates are less reactive[10] and this method was decidedly inferior to (a) for the preparation of IV. Method (c) was satisfactory for the synthesis of an α-bromosulfone (V) for which the other methods were not applicable. This was a rather laborious method, however, because it required the synthesis of the α-sulfonyl acid. Furthermore, the bromination of α-*p*-tolylsulfonylacetic acid could not be stopped at the monobromo stage and a dibromosulfone (VI) was produced. Considering the limitations mentioned for these three methods, it may be noted that at least one of them should be satisfactory for the synthesis of any α-bromosulfone.

The reactions of the α-bromosulfones show that the sulfone group increases the reactivity of the halogen in oxidation reactions; that is, the halogen is "positive"[5] in character. For example, the sulfonylmethyl bromides gave sulfonylmethanes when treated with phenylmagnesium bromide,[12] the sodium salts of *n*-butyl mercaptan and *p*-thiocresol or sodium ethoxide. The other products were bromobenzene, disulfides and aldehyde resins, respectively. Similar reactions have been observed[13] with other types of positive halogen compounds. The α-bromosulfones did not oxidize hydrazine or hydriodic acid under the conditions previously used.[7]

$$RSO_2CH_2Br \xrightarrow{C_6H_5MgBr} C_6H_5Br + [RSO_2CH_2]MgBr \xrightarrow{HOH} RSO_2CH_3$$

$$RSO_2CH_2Br \xrightarrow{RSNa} RSO_2CH_3 + RSSR + C_2H_5ONa$$

$$RSO_2CH_2Br \xrightarrow[C_2H_5ONa]{C_2H_5OH} RSO_2CH_3 + NaBr + CH_3CHO(polymer)$$

With pyridine, the sulfonylmethyl bromides were largely unchanged but small amounts of disulfonylethanes were isolated. This novel dehalogenation is quite different from that previously noted[7] with α-bromo-α-sulfonylamides.

$$2RSO_2CH_2Br \xrightarrow[C_5H_5N]{-2Br} RSO_2CH_2CH_2SO_2R$$

The α-bromosulfones, except in reactions involving oxidation–reduction, were unusually inert. They were recovered unchanged from treatment with tetrahydroquinoline, dimethylamine, alcoholic silver nitrate, sodium acetate and sodium cyanide. Since the α-bromosulfones are less reactive than alkyl bromides with these reagents, it may be concluded that the sulfone group is a deactivating group so far as these reactions are concerned. While this may be a specific property of the sulfone group, it may be pointed out that the reactions of α-bromosulfones are actually exaggerated examples of a trend noted with α-haloketones.[14] It therefore seems probable that the increased reactivity generally attributed to the halogen of α-haloketones, esters, etc., may be due to an initial reaction of the reagent with the unsaturated group. This may be interpreted as support for a similar opinion[3] concerning the reactions of α-haloketones and as an indication that this view may be extended to the α-halo derivatives of unsaturated compounds in general.

## Experimental Part[15]

**Sodium *n*-Butanesulfinate.**[16]—*n*-Butyl mercaptan (214 ml., 180 g.) was added to a sodium ethoxide solution prepared by dissolving 46 g. of sodium in 650 ml. of absolute alcohol. A solution of 220 g. of ethylene bromide in 100 ml. of absolute alcohol was added with stirring over a period of about twenty minutes at a rate which caused the reaction mixture to reflux gently. The mixture was refluxed with stirring for one hour, allowed to stand overnight and the alcohol removed by distillation. The residue was poured into cold water, the oil separated and the aqueous layer extracted with two 100-ml. portions of ether. The ether extracts were combined with the oil, dried over calcium chloride and the solvent removed by distillation. The residue of crude 1,2-di-*n*-butylthioethane was dissolved in 500 ml. of acetic acid–acetic anhydride solution (1:1) and the solution chilled in an ice–salt-bath. Five hundred fifty grams of 30% hydrogen peroxide was added with stirring over a period of about two hours at such a rate that the temperature remained between 20 and 40°. After the reaction mixture had stood for two days the crystals were removed by filtration through a Buchner funnel without paper and washed with water. The filtrate was poured into three times its volume of water and allowed to stand for several hours. The solid was washed with water and dried. The combined solids

(12) Kohler and Tishler[6] reported a similar reaction with diphenylsulfonyldibromomethane.

(13) (a) Biltz and Behrens, *Ber.*, **43**, 1984 (1910); (b) Fisher, Oakwood and Fuson, *J. Am. Chem. Soc.*, **52**, 5036 (1930); Kohler and Tishler, *ibid.*, **54**, 1594 (1932); (c) Kohler and Potter, *ibid.*, **58**, 2166 (1936); (d) Ziegler and Connor.[7]

(14) For example, phenacyl halides do not react with alcoholic silver nitrate [Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1935, p. 23]. α-Bromo derivatives of mesityl ketones, in which addition to the carbonyl is hindered, do not react with sodium acetate, react slowly with amines [Babcock, Nakamura and Fuson, *J. Am. Chem. Soc.*, **54**, 4407 (1932)] and give bromobenzene with phenylmagnesium bromide.[11b]

(15) Melting points are corrected.

(16) This preparation was suggested by the reaction reported by Otto, *J. prakt. Chem.*, [2] **30**, 361 (1884).

weighed 248 g. (92%), m. p. 177–179°. Recrystallization from alcohol–acetic acid (3:1) gave pure 1,2-di-*n*-butylsulfonylethane melting at 180–181°.[17]

To 172 g. of the crude disulfone in 360 ml. of 50% alcohol was added 175 g. of potassium cyanide and the mixture refluxed for twenty-four hours. About 185 ml. of solvent was removed by distillation, the residue diluted with 200 ml. of water and 480 ml. of 6 *N* hydrochloric acid added slowly, using an aspirator to remove the hydrogen cyanide liberated. The solution was extracted with five 200-ml. portions of ether and the combined extracts washed repeatedly with 50-ml. portions of 10% sodium hydroxide solution. When the extracts were alkaline, the ether layer was washed once more, the combined aqueous extracts neutralized with sodium bicarbonate, decolorized first with 20 g., then 10 g., of charcoal and evaporated to dryness. The residue was dissolved in about 150 ml. of alcohol, filtered and the filtrate evaporated until solid appeared. After chilling overnight in a refrigerator the solid was removed by filtration, washed with a little cold alcohol and dried. This product weighed 51 g. Evaporation of the filtrate gave an additional 73 g. The combined products corresponded to 72% of the theoretical amount of sodium *n*-butanesulfinate, based on the disulfone used. The product was characterized by reaction with chloroacetamide to give *n*-butylsulfonylacetamide.[18]

***n*-Butylsulfonylmethyl Bromide (III).**—To 28 8 g. of sodium *n*-butanesulfinate (obtained from the mother liquor of the reaction described above) dissolved in 150 ml. of alcohol was added 42.6 g. of methylene bromide. The mixture was heated for twenty hours on the water-bath, the alcohol removed by distillation and the residue extrated with benzene. The benzene was distilled and the residue recrystallized from ligroin (b. p. 70–90°). The yield of pure III was 19 g. (44%), m. p. 47–48°.

*Anal.* Calcd. for $C_5H_{11}SO_2Br$: Br, 37.2. Found: Br, 37.2, 37.4.

***p*-Tolylsulfonylmethyl Bromide (IV).**—To 0.20 mole of ethylmagnesium bromide in 40 ml. of ether was added a solution of 27.2 g. of methyl *p*-tolyl sulfone[19] in 150 ml. of benzene. After the evolution of ethane had ceased an additional 100 ml. of benzene was added and the mixture refluxed for three minutes. Twenty-four grams (0.15 mole) of bromine in 50 ml. of benzene was added while in an ice-bath. The mixture was vigorously stirred to prevent the formation of a lump. After stirring for two hours at room temperature the material was poured into 150 ml. of water. The excess bromine was removed by the addition of a solution of sodium bisulfite and the benzene layer separated and evaporated to 100 ml. After cooling overnight, the crystalline solid was removed by filtration and the filtrate again concentrated. The solid obtained by the latter concentration was brown and was decolorized by treatment with charcoal in alcoholic solution. The solid obtained in this manner was combined with the initial solid from the benzene layer and the combined materials recrystallized from alcohol. The yield of pure IV was 20 g. (50%), m. p. 89–90°.[8]

Reaction of sodium *p*-toluenesulfinate with methylene bromide was carried out as described above for the preparation of III. After removal of the alcohol the residue was poured on water and the solid recrystallized from alcohol. The yield was 17.5 g. (33%), m. p. 90–91°.[8]

Attempts to halogenate methyl *p*-tolyl sulfone with bromine, sodium hypobromide and *t*-butyl hypochlorite under conditions previously reported for α-bromo-α-sulfonylamides[7] were unsuccessful and 75–85% of the starting material was recovered unchanged.

**α-*n*-Butylsulfonyl-*n*-propyl Bromide (V).**—To a mixture of 25 g. of α-bromo-*n*-butyric acid and 75 ml. of water, sodium carbonate was added until a homogeneous solution, neutral to litmus, was obtained. Then 22 g. of sodium *n*-butanesulfinate was added and the solution refluxed for four hours. The reaction mixture was acidified with 6 *N* hydrochloric acid and extracted with one 75-ml. and two 50-ml. portions of ether. After removal of the solvent from the combined extracts by distillation, the residue was chilled but would not solidify. The oil was then dissolved in 25 ml. of water containing a slight excess of sodium carbonate and this solution added to a solution of 24 g. of bromine in 75 ml. of 20% sodium hydroxide at 0°. The solution was placed in a refrigerator for four hours and then allowed to stand at room temperature overnight. It was then acidified and refluxed until the bromine color was removed. During this procedure some gas was evolved. The mixture was extracted with one 75-ml. and two 50-ml. portions of ether. The ethereal solution was dried over magnesium sulfate, the ether removed and the oil chilled overnight. Since the product did not solidify, it was subjected to vacuum distillation and a fraction collected boiling at 127–142° (5 mm.). There was some decomposition when the bath reached 160°, before any distillate was obtained. This may have been due to decarboxylation of the α-sulfonyl-α-bromoacid. The product was redistilled and 8.9 g. (25% based on α-bromobutyric acid) of pure V obtained, b. p. 133–136° (5 mm.).

*Anal.* Calcd. for $C_7H_{15}O_2SBr$: Br, 32.9. Found: Br, 32.7, 32.6.

***p*-Tolylsulfonyldibromomethane (VI).**—To 5.7 g. of α-*p*-tolylsulfonylacetic acid[20] was added 300 ml. of 5% sodium hydroxide solution and the solution chilled to 5°. After the addition of 1.45 ml. of bromine the mixture stood for one and one-half hours in a refrigerator and was then warmed until the solid coagulated. The product was washed with cold water and recrystallized from alcohol. The yield was 3.2 g. (70%) of material melting at 116–117°.[21]

**Reaction with Sodium Mercaptides.**—To a sodium ethoxide solution prepared by dissolving 0.71 g. of sodium in 70 ml. of alcohol was added 3.2 ml. of *n*-butyl mercaptan. This solution was cooled in an ice-bath, 7.6 g. of *p*-tolylsulfonylmethyl bromide added, and the mixture allowed to come to room temperature as the ice melted. After standing at room temperature for five days most of the alcohol was removed under diminished pressure and the residue poured on ice. The solid was recrystallized from ether, then ligroin–ether (3:1) mixture and identified as methyl *p*-tolyl sulfone by a mixed melting point with an authentic specimen. The yield was 4.0 g. (76%) of I, m. p. 82–85°.

(17) Whitner and Reid, *J. Am. Chem. Soc.*, **43**, 640 (1921).
(18) d'Ouville and Connor, *J. Am. Chem. Soc.*, **60**, 33 (1938).
(19) Shriner, Struck and Jorison, *ibid.*, **52**, 2060 (1930).
(20) Gabriel, *Ber.*, **14**, 833 (1881).
(21) This compound was previously prepared by Otto.[8]

Under similar conditions 2.5 g. of *p*-thiocresol and 4.3 g. of *n*-butylsulfonylmethyl bromide gave ditolyldisulfide and a product which did not crystallize. Recrystallization of the disulfide from alcohol gave 2.25 g. (90%), m. p. 45–46°.

**Reaction with Phenylmagnesium Bromide.**—To a solution of 0.15 mole of phenylmagnesium bromide in 70 ml. of ether was added with vigorous stirring a solution of 34.8 g. of IV in 400 ml. of ether. The addition required about one-half hour and the reaction mixture was refluxed an additional three hours, stirred for two hours without heating, and allowed to stand overnight. The residue remaining after filtration was washed with ether, suspended in iced hydrochloric acid and recrystallized from alcohol. The yield was 14.3 g. (56%) of methyl *p*-tolyl sulfone, m. p. 84–86°. The ether was removed from the filtrate of the reaction mixture by distillation from a water-bath through a fractionating column. The distillation residue was mixed with a little ether and ligroin (b. p. 70–90°) was added. The organometallic compound remaining was treated as before and gave 1 g. (3%) of IV. The ether–ligroin solution upon fractionation gave 18.2 g. (77%) of bromobenzene, b. p. 154–157°.

**Reaction with Pyridine.**—A solution of 12.5 g. of IV and 4.7 g. of pyridine in 100 ml. of absolute alcohol was refluxed for forty hours and the alcohol removed by distillation. The residue was diluted with 200 ml. of ether and the solid recrystallized from alcohol. This gave 1 g. (8%) of 1,2-di-*p*-tolylsulfonylethane, m. p. 201–202° which was identified by a mixed melting point with an authentic sample.[16] The ethereal solution was evaporated and the solid residue recrystallized from alcohol. This gave 9 g. (72%) of unreacted IV, m. p. 89–90°.

A similar experiment in which 2.15 g. of III was refluxed with pyridine in 25 ml. of alcohol for twenty-two hours gave 0.05 g. (2%) of 1,2-di-*n*-butylsulfonylethane, m. p. 177–179°, and 2.05 g. (95%) of unchanged III, m. p. 47–48°.

**With Sodium Ethoxide.**—To a sodium ethoxide solution prepared by dissolving 0.92 g. of sodium in 100 ml. of absolute alcohol was added 10 g. of IV and the mixture refluxed for fifteen hours. The solution was cooled, filtered and the solid washed with a little cold alcohol and then with water. There remained 0.2 g. of yellow, highly insoluble material which was not investigated further.[22] The alcoholic solution gave 5 g. (74%) of methyl *p*-tolyl sulfone, m. p. 85–86°, which was identified by a mixed melting point.

**Other Results.**—The recovery of unchanged bromosulfone was 80–95% in the following tests: (a) heating IV with two equivalents of tetrahydroquinoline at 100° for sixteen hours, (b) treatment of IV with two equivalents of dimethylamine for five days at room temperature and five hours at 40–50°, (c) refluxing IV for forty hours in 75% alcohol with two equivalents of potassium cyanide, (d) refluxing III for seven hours with two equivalents of sodium acetate in alcohol solution. No iodine was liberated when III and IV were treated with acidified potassium iodide under the conditions previously described.[7] No reaction occurred between III or IV and hydrazine hydrate under the conditions previously used[6] but VI reacted slowly, giving 3 ml. (8%) of nitrogen in five hours from 0.5 g. of the dibromosulfone.

## Summary

Syntheses of three α-bromosulfones and one α,α-dibromosulfone have been described. The reactions of the α-bromosulfones showed that the sulfone group activates the halogen for oxidation reactions but deactivates it in metathesis reactions. The results suggest that the increased reactivity generally attributed to α-bromo-ketones, esters, etc., is due to preliminary reaction of the reagent with the unsaturated group, rather than to the polar influence of the group.

(22) This material was probably aldehyde resin. Willstätter and Hattenrote [*Ber.*, **43**, 1984 (1910)] reported the formation of aldehyde resins from the oxidation of alcohol by N-chloro compounds in which the hypochlorite character of the halogen is well known.